

Author's Response

Sir:

Thank you for the comments regarding our article *A fatal drug interaction between oxycodone and clonazepam*. The commentary states that the authors seem to base their statement of a fatal drug interaction on a metabolic interaction between oxycodone and clonazepam. The second paragraph of the introductory section postulates not only mechanisms of metabolic hindrance by competitive substrates (clonazepam and oxycodone), but also by other drugs (cannabinoids) and pathologies present in this particular subject. In our conclusions, we also state the concentrations of oxycodone and clonazepam observed may have resulted from either an acute administration of a particular dosage and/or an attenuated metabolism.

The commentary noted that we suggested the competitive inhibition of CYP3A4 by clonazepam. First, competitive inhibition of CYP3A4 does not mean inactivation of or decreased activity of the enzyme. It is the reduction of availability of CYP3A4 to another substrate due to the fact that its activity is being occupied by a high concentration of its primary substrate. If availability of CYP3A4 to oxycodone is decreased, this may lead to a higher oxycodone concentration. Second, the reduction of CYP3A4 availability is also known to occur with cannabinoids and hepatic pathologies (1). It was noted that no reports indicate that clonazepam is a CYP3A4 inhibitor. Clonazepam isn't an inhibitor (meaning deactivator in this sense) but a substrate to CYP3A4 (2). In regards to the point of not knowing if inhibiting CYP3A4 increases oxycodone concentrations; it is what we postulated had occurred based on the logic that if the availability of CYP3A4 is decreased, less oxycodone can be metabolized. The commentary stated that it is not established that CYP3A4 mediates the metabolism of oxycodone. Indeed, oxycodone metabolism by CYP3A4 produces an N-demethylation to yield noroxycodone (3).

The commentary referenced the article by Heiskanen et al. to show the inhibition of CYP2D6 did not cause a change in the pharmacodynamic effects of oxycodone. It should be noted in the referenced paper the pharmacodynamic effects were measured by the following subjective symptoms, the Maddox Wing test, Digit Symbol Substitution, Critical Flicker Fusion test and Cogan pupillometry. Analgesia nor respiratory depression were assessed in this study. Psychomotor impairment generally occurs at lower blood concentrations of oxycodone than does respiratory depression. This particular investigation that noted no change in psychomotor impairment was conducted with lower dosages (20 mg) than the calculated *minimum* dosage taken by the deceased in our case study. Therefore we cannot state that the pharmacodynamic effect of respiratory depression would not be affected by CYP2D6 inhibition. Another explanation may be, as previously stated, that cross reactivity of CYP450 isoenzymes allows for "shunting" of metabolism from one isoform to the other. Therefore at higher concentrations of oxycodone, the importance of the role of the CYP2D6 isoform may be diminished.

It was noted in the commentary that the CYP450 isoenzyme may have been diminished at baseline and there is no evidence to support enzyme inhibition as a mechanism of toxicity. We agree, due to the liver pathologies, the victim may have had diminished CYP450 levels and therefore may have been a contributing factor to the overall decrease in available enzyme for oxycodone metabolism, this was stated in our conclusion. Enzyme inhibition in and of itself would not be a direct mechanism of toxicity, but having the enzyme inhibited would allow for a decreased rate of oxycodone metabolism leading to sustained higher blood concentrations.

It was suggested that the victim would likely have a tolerance to opiates due to previous drug abuse and would be able to tolerate higher concentrations of oxycodone and therefore one should not correlate a fatal pharmacodynamic effect based on a blood level alone because of the tolerance. If this case only involved oxycodone, we may be in agreement. However, this paper does not correlate a fatal pharmacodynamic effect solely to oxycodone. The fatal outcome was due to the additive to synergistic effects of two drugs (clonazepam and oxycodone). The commentary states that no specific conclusions regarding pharmacologic effects can be drawn solely from the measured concentrations. Agreed, hence the statement in the conclusion of our paper "based on pathological and laboratory findings..."

It was suggested that the synergistic CNS depression is a result of the intended pharmacological effects of the medications, not a drug interaction and that each drug alone could have caused the patients demise. In response, from the commentary, "The concept of a drug interaction implies that a pharmacokinetic or pharmacodynamic effect has occurred that would not occur with either drug alone." Also, the reader stated the victim was most likely an opioid tolerant individual. It is therefore unlikely that the toxic concentration of oxycodone found would have been *fatal* by itself in this person. We cannot conclude that the clonazepam concentration would be fatal by itself. Deaths due to benzodiazepines alone are extremely rare and are almost exclusively found with the more potent benzodiazepines such as alprazolam (4). The mechanism of action of benzodiazepines is to potentiate the effects of GABA. And GABA assists in hyperpolarizing the neuron by increasing the influx of chloride, thus increasing the activation energy required to depolarize the neuron. This method of hyperpolarization has its finite limits (e.g., a finite amount of chloride can be transported into cell before the concentration gradient forces the chloride to "leak" out). The relative safety of benzodiazepines lies in their mechanisms. The drug "interaction" lies both in the competitive inhibition of the metabolic enzymes involved AND the additive to synergistic effects of the combined drugs with different mechanisms of depression on the CNS.

Regarding the discrepancy concerning the number of prescriptions written for oxycodone in 2000, this was a typographical error. The intended statement was to be written as "...nearly 6 million prescriptions..." (5).

References

1. Ghosh SK, Poddar MK. Effect of delta-9-tetrahydrocannabinol and theophylline on hepatic microsomal drug metabolizing enzymes. *Biochem Pharmacol* 1992 Nov 17;44(10):2021-7. [PubMed]
2. Hardman JG, Limbird LE, editors, Goodman and Gilman's the pharmacological basis of therapeutics. 10th ed. McGraw Hill, 2001;406.
3. Quantitative contribution of CYP2D6 and CYP3A4 to oxycodone oxidation in human liver microsomes. Presented at the American Assoc. of Phar